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10/666,535	09/22/2003	Hideki Ichikawa	2923-0562	5882

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/10/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/666,535	**Applicant(s)** ICHIKAWA ET AL.	
	Examiner David S. Romeo	**Art Unit** 1647	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 April 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): The rejection of claim 10 under 35 U.S.C. § 112, second paragraph.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-14*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

David S Romeo
Primary Examiner
Art Unit: 1647

Continuation of 11. does NOT place the application in condition for allowance because:
Claims 1-7 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neidhardt (WO 93/16099) in view of Ron (U. S. Patent No. 5,171,579) and Avis (1990).
Applicants argue that:

The Avis reference provides a general discussion of lyophilization but has
nothing to do with proteins in particular. Many substances are indicated as being possible agents to make the dried-product plug occupy essentially the same volume as that of the original solution. The disclosure of Avis would not have guided one skilled in the art to select mannitol for use with MP52 from the numerous recited substances. As discussed in prior responses, applicants have found that products used in the prior art were not successful when used with MP52 and thus the use of specific substances is not predictable from the general disclosure in the cited prior art.

Applicants' arguments have been fully considered but they are not persuasive. The examiner considers applicants' arguments a piecemeal analysis of the Avis reference. Avis must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole. According to Avis, one skilled in the art of lyophilization typically considers "the nature and stability characteristics required during the liquid state, both freshly prepared and when reconstituted for use, [as well as] the characteristics desired in the dried plug" (Avis, page 1566), when formulating a pharmaceutical or biological product. More to the point, Avis identifies the choice of excipient as a variable affecting the characteristics of the lyophilized product, i.e., "whether the lyophilized substance will be dull and spongy or sparkling and crystalline, firm or friable, expanded or shrunken, etc." (Avis, page 1566). It is fair to say that Avis identifies the choice of excipient as a result effective variable, and the identification of mannitol as the ideal lyophilization excipient for MP52 would have been within the ordinary skill in the art. Furthermore, patentability requires novelty and unobviousness in light of the prior art, not in light of what applicants knew and included in their patent application.

Applicants argue that:
Ron does not cure the deficiencies in Avis as Ron does not suggest that mannitol is suitable for the use in a lyophilized product of MP52 either. Ron generally suggests that additional optional components such as cryogenic protectors might be useful. However, no examples were carried out in order to show that mannitol is in fact suitable in the connection with osteogenic proteins. Mannitol tends to form crystals during freezing and to leave the protein exposed (Williams NA, Lee Y, Polli GP, et al., "The Effects of Cooling Rate on Solid Phase Transitions and Associated Vial Breakage Occurring in Frozen Mannitol Solutions," J Parent Sci Tech, 40:135-141, 1986). Mannitol has also been found to provide little biological protection during freezing since it crystallizes and is thereby removed from the preparation (Gerald D. J. Adams, J. Richard Ramsay, Optimizing the lyophilization cycle and the consequences of collapse on the pharmaceutical acceptability of erwiniaL-Asparaginase, http://www3.interscience.wiley.com/cqi-bin/abstract/72505070/ABSTRACT). The suggestion of mannitol as a possible cryogenic protector does not show that mannitol is in fact successful and it was unpredictable from Ron whether or not the use of mannitol would be helpful in context with a lyophilized MP52 product. Though MP52 and BMP-2 belong to the same protein family, as previously pointed out, they do not exhibit identical physical behavior. Properties such as solubility cannot be transferred from one protein to another since individual amino acids on the protein surface have different hydrophobicity and can also show different solution behavior and different tendencies to aggregation. In general, it is not possible to transfer data from one protein to another even if they are in the same family. Thus, even if Ron had shown that mannitol acts as a cryogenic protector of BMP-2, which he did not, one would not assume that mannitol could also be used with MP-52. Since not all cryoprotectants can be used with all proteins, applicants contend that one skilled in the art would not reasonably expect mannitol to be useful with MP52 without testing. In view of the above discussion, applicants request that this rejection be withdrawn.

Applicants' arguments have been fully considered but they are not persuasive. The Williams and Ramsay references are not of record. The examiner cannot consider evidence that is not of record. Furthermore, applicants have not provided a showing of good and sufficient reasons why this evidence was necessary and was not earlier presented. Furthermore, applicants have not explained the relevance of differences in solubility in basic amino acids, e.g. lysine, between BMP-2 and MP52 to lyophilization in mannitol. Obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. Ron contains the suggestion to modify Neidhardt to produce the claimed invention, and Avis contains the evidence suggesting the modification would be successful. The references, taken as a whole, would have suggested applicants' invention to one of ordinary skill in the art at the time the invention was made.

Claims 7-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neidhardt (WO 93/16099) in view of Ron (U. S. Patent No. 5,171,579) and Avis (1990) as applied to claims 7 and 12-14 above and further in view of Chang (J Pharm Sci. 1996 Dec;85(12):1325-30).

Applicants argue that:
As discussed in applicant's prior response, Chang does not cure the deficiencies in Neidhardt, Ron and Avis as Chang also shows that no general predictions can be made about the lyophilization conditions for specific proteins. Chang, on page 1325, first column, discloses that "despite the numerous freeze-thawing studies on proteins, the choice of these solutes and development of stable formulations is still largely empirical because of the lack of a full understanding of the relative importance of the various stresses arising during freezing and of mechanisms by which additives protect proteins against these stresses". In other words, for every protein, optimum conditions must be determined individually and cannot be predicted from the results obtained with other proteins. In view of the above discussion, applicants request that this rejection be withdrawn.
Applicants' arguments have been fully considered but they are not persuasive. The examiner believes that the comments in Chang referred to by applicants are Chang's introductory comments directed to the problems which Chang addresses in the experiments that follow. Chang's results indicate that the freezing-induced denaturation is related to the exposure of proteins to an ice-water

interface, so it seems rational to use surfactants as cryoprotectants (page 1327, right column, full paragraph 2). Chang teaches that the addition of small amounts of surface-active agents protected proteins from both freeze- and surface-induced denaturation (Abstract). The capacity of 0.01% Tween 80 to protect proteins during freeze-thawing appears to be quite general because all of the model proteins were essentially completely protected (paragraph bridging pages 1327-1328). To determine how general this protective effect was, the influence of several surfactants, with different chemical structures, on freeze denaturation of LDH was tested. All the tested surfactants protected LDH from precipitation during a quench-freezing process, even though the control frozen without a surfactant showed a significant increase in turbidity (Table 2). See page 1328, left column, full paragraph 1. The surfactants tested included Tween, Triton, and Brij. See page 1328, Table 2. This general stabilization of proteins during freeze-thawing by relatively low concentrations of surfactants strongly supports the contention that damage to proteins during freezing is due, at least to a large degree, to surface denaturation (page 1328, left column, full paragraph 2). A surfactant may only be sufficient to protect proteins during the freezing step. Another stabilizer, which is known to confer protection during drying (e.g., sucrose) will probably be needed to completely inhibit protein unfolding during freeze-drying. See page 1329, right column, last paragraph. It is fair to say that Chang identifies the addition of surfactants and their combination with another stabilizer which is known to confer protection during drying, as a "result effective variable" for inhibiting protein denaturation during freeze-drying. Therefore, Chang contains specific guidance regarding the addition of surfactants during the freeze-drying process, a suggestion to modify Neidhardt in view of Ron and Avis to produce the claimed invention, and evidence suggesting the modification would be successful.

Applicants point out that the argumentation in applicant's prior response regarding mixing ratios included a clerical error. Applicants remarks stated that "22 mg of BMP-2 and 8 mg of mannitol were used, i.e. a mixing ratio of 1:364". This should have stated "22 µg of BMP-2". In any case, a skilled artisan would have assumed that BMPs are used with considerably higher dosages of mannitol than is the case according to the present invention with MP52 wherein the optimum mixing ratio from 1:5-50 is sufficient.

Applicants' arguments have been fully considered but they are not persuasive. The examiner believes he correctly construed applicants' previous arguments as being directed to "22 µg of BMP-2". Avis teaches that mannitol has been found to be most useful to increase the solids content of the original solution to between approximately 5 and 25% so that the freeze-dried product plug occupies essentially the same volume as that of the original solution (page 1566, column 2, full paragraphs 1-3). A 5 to 25% mannitol solution contains 50 to 250 mg mannitol per ml. A solution comprising 2 to 4 mg/ml MP52 and 50 to 250 mg/ml mannitol is a solution comprising MP52 and mannitol in the range of 1 : 5-50 (ratio by weight). A lyophilized form of said solution is a composition comprising MP52 and mannitol in the range of 1 : 5-50 (ratio by weight).

Claims 7-10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neidhardt (WO 93/16099), Ron (U. S. Patent No. 5,171,579), and Avis (1990) as applied to claims 7 and 12-14 above and further in view of Chang (J Pharm Sci. 1996 Dec;85(12):1325-30) and further in view of Hansen (U. S. Patent No. 6,586,574) and in light of the MeSH definition of "poloxamer."

Applicants argue that:
As discussed above, the combination of Neidhardt, Ron, Avis and Chang, does not suggest that mannitol should be used when lyophilizing MP52. Hansen is cited only for the disclosure of surfactants for stabilization of freeze-dried proteins and does not cure the deficiencies in Neidhardt, Ron, Avis and Chang regarding the use of mannitol with MP52 in a lyophilized composition. In view of the above discussion, applicants request that this rejection be withdrawn.

Applicants' arguments have been fully considered but they are not persuasive. Hansen was not cited by the examiner in order to cure any alleged deficiencies in Neidhardt, Ron, Avis and Chang regarding the lyophilization of MP52 with mannitol. The examiner believes that he has already adequately addressed these alleged deficiencies. One of ordinary skill in the art would be motivated to modify Neidhardt, Ron, Avis and Chang with Hansen because further stabilization of freeze-dried proteins can be obtained by the addition of surfactants, such as poloxamers, as taught by Hansen..